REMARKS

Rejections for obviousness-type double patenting

The Examiner has maintained the rejection of claims 1-5, 8, 10-12, 14-16, 20-21 and 23 for double patenting over U.S. '176 combined with Landegren (1993). As in previous actions, the Examiner maintains that the claims of the invention differ from the claims of U.S. '176 only in the final extension step (iv). The Examiner relies on Landegren (1993) as teaching the use of PCR in DNA detection assays.

In response to Applicants' arguments that Landegren (1993) teaches the use of PCR/DNA amplification for improving the sensitivity of DNA detection assays, whereas the present assay does not use the final step for improving sensitivity, the Examiner notes that under U.S. patent practice the motivation to combine two references to achieve the invention can be different from that of the inventors. With the instant invention, the Examiner takes the position that even if the inventors included step iv) in the present method for a reason other than improving sensitivity, one skilled in the art would be motivated to use the same step for the purpose of improving sensitivity. The Examiner concludes that the amplification step (iv) would be the same whether used to improve sensitivity as taught by Landegren (1993) or to analyze the

fragments generated in steps (i) to (iii). Applicants traverse this rejection and withdrawal thereof is respectfully requested.

As noted above, the Examiner asserts that the invention differs from the claims of U.S. '176 only in the final extension step (iv). However, the Examiner's conclusion about the differences between the claims of U.S. '176 and the present invention is incorrect because the present invention further differs from U.S. '176 in step iii), "cleaving the DNA at the abasic site so as to generate and release an extendible upstream DNA fragment having a 3'-OH terminus, wherein the specificity of the extendible fragment is determined by the sequence of the target nucleic acid."

The claims of U.S. '176 recite as step iii) "cleaving phosphate linkages at abasic sites generated in step ii)". There is no recitation in the claims that an extendible upstream DNA fragment having a 3'-OH terminus would be generated by the cleavage. Turning to the specification of U.S. '176 to determine whether it was contemplated that the cleavage would generate an extendible upstream DNA fragment having a 3'hydroxyl terminus, one skilled in the art would conclude that the cleavage that is required by the present claims had not been contemplated in U.S. '176.

U.S. '176 is silent with regard to any explicit discussion regarding the nature of the 3′ end of the cleavage product generated by the cleavage at the abasic site. The absence of any discussion regarding the 3′ end of the cleavage product is evidence that the nature of the 3′ end was no importance to the reference methods. In addition, when the cleavage methods disclosed in U.S. '176 are considered it is evident that there was no contemplation in U.S. '176 of cleaving the DNA at the abasic site so as to generate and release an extendible upstream DNA fragment having a 3′ hydroxyl terminus. All of the Examples in U.S. '176 disclose the use of alkali treatment for cleavage. See for example, Example 4, at column 16, lines 34-36 and Example 5 at column 17, lines 55-57. In addition, U.S. '176 states at column 9, lines 10-13, that "Preferably the phosphate linkages at the abasic site are cleaved by a treatment selected from alkali treatment...." Similarly, column 9, line 35, states "The preferred treatment is alkali at high temperature,..." Reading the specification of U.S. '176, one skilled in the art would conclude that the preferred method of cleavage at the abasic sites in the methods of U.S. '176 is with alkali treatment. However, alkali treatment results in a blocked 3′ end of the cleavage product, which could not be used in the presently claimed method.

While the reference does disclose that as an alternative, an endonuclease may be used, there is no disclosure in U.S. '176 that the cleavage must be such that a free 3′ hydroxyl group that can be extended as a primer with a new specificity is generated and it is clear that the preferred method of cleavage is alkali treatment, which results in a blocked 3′ end. As such, the present claims differ from the claims and disclosure of U.S. '176 in more than step iv). Step iii) of U.S. '176 would not function with step iv) of the invention, because step iii) of U.S. '176 does not result in an extendible upstream DNA fragment having a 3′-OH.

The Examiner further relies on Landegren for teaching the use of PCR in DNA detection assays. However, as discussed above, the present invention differs from U.S. '176 in more than the use of PCR as a detection method. As discussed above, the present invention provides a method for generating new primers with new specificities or primers with new 3′ specificities, wherein the new specificity is determined by the sequence of the target nucleic acid. In addition, with the method of the invention, the character of the new specificity is determined by extending the primers having the new specificities or primers with new 3′ specificities on a template nucleic acid. The method of the present invention is dependent on the generation of an extendible upstream DNA fragment having a 3′-OH terminus, upon cleavage at the abasic site in step

iii). As noted above, U.S. '176 teaches that the cleavage at the abasic site results in a blocked 3'-OH end. There is no disclosure or suggestion in U.S. '176 of cleaving at the abasic site so as to generate an extendible upstream DNA fragment having a 3'-OH terminus. Nor is there any such disclosure in Landegren. As such, the present invention is not achieved when the references are combined and the present claims are not obvious over the claims or disclosure of U.S. '176 combined with Landegren and withdrawal of the obviousness-type double patenting rejection is respectfully requested.

Rejections under 35 U.S.C.§102(b)

The Examiner again maintains the rejection of claims 1-21 and 23 as being anticipated by Dianov et al. (1992). The Examiner notes, in part, that Dianov et al. encompasses the performance of additional steps. Applicants traverse this rejection and withdrawal thereof is respectfully requested.

Dianov et al. pertains to a basic research study regarding the mechanism of DNA repair at abasic sites. Thus, Dianov et al. has nothing to do with DNA sequence analysis. Dianov et al. does show that a new 3' extendible end can be created within a synthetic piece of DNA. However, the new 3' extendible end that is generated in Dianov et al. does not have a new specificity that is determined

by the target nucleic acid. Nor would such a new specificity be possible with Dianov et al., since the new 3′ end can only be created within the synthetic piece of DNA. Thus, the methods disclosed in Dianov et al. could not be used to generate primers with new specificities or primers with new 3′ specificities that are determined by the sequence of the target nucleic acid. To make this feature more evident in the claims, claim 1 has been amended in step iii) to recite,

> cleaving the DNA at the abasic site so as to generate and release an extendible upstream DNA fragment having a 3′ hydroxyl terminus, **wherein the specificity of the extendible fragment is determined by the sequence of the target nucleic acid**

Thus, the present invention is clearly distinguished from any inadvertent overlap with the completely unrelated disclosure of Dianov et al. Withdrawal of the rejection is, therefore respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong, PhD (Reg. No. 40,069) at the telephone number of the listed below.

Applicants request a three (3) month extension of time for filing the present response. The required fee is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
MaryAnne Armstrong, PhD #40,069

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

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